do what about them; and then do what all will have agreed must be done. The disordered approach of the last decade or more simply has not worked well, nor is it likely that it ever will.

—MSMW

Evaluation of Asymptomatic Patients

PERIODIC HEALTH EXAMINATIONS (PHE's) are carried out in asymptomatic patients in an effort to prevent disease or to identify it at a very early stage. These encounters have contributed to a more complete patient data base and have facilitated physician-patient rapport, factors identified with improved patient care. A large, prospective study showed that death rates from certain "potentially postponable" disorders—such as hypertension and carcinoma of the colon—are reduced in those receiving PHE's.[1] Nonetheless, opponents have charged that the purported benefits of PHE's are not supported by firm scientific data.

Two recent reports provide PHE guidelines and shed light on the aforementioned criticism. An American Cancer Society report details recommendations for a "cancer-related checkup."[2,3] The report of the Canadian Task Force on the Periodic Health Examination[4] reviews the effectiveness of prevention and treatment of 78 conditions and lists recommendations based on sex, age and risk category.

In general, the recommendations point toward a "streamlined" PHE. For example, the American Cancer Society now advises that women over the age of 20, and those under 20 who are sexually active, have a Pap test "at least every three years, but only after they have had two negative Pap tests a year apart." The same report no longer recommends annual x-ray studies of the chest for the detection of lung cancer.

It should be noted that both reports have stirred controversy. Critics have observed that the guideline for x-ray studies of the chest is premature and in part based on preliminary data from ongoing prospective studies. The report of the Canadian Task Force does not recommend a "complete history and physical examination." This report refers to the studies on which its recommendations are based. For many crucial questions it is noteworthy that pertinent data are not available; hence the recommendations are often merely a summary of "expert opinion."

While physicians may take issue with specific recommendations, these reports merit careful study. Individual practitioners can then formulate PHE guidelines that are best suited for their patients. This will contribute to improved care and more efficient use of the health care dollar.

JOHN H. HOLBROOK, MD
Special Editor for Utah
Associate Professor
Department of Internal Medicine
University of Utah Medical Center
Salt Lake City

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Adenomatous Colonic Polyposis: To Lump or to Split?

WITH AN INCIDENCE of about one per 8,000 population, the familial polyposis disorders occur often enough that most physicians will encounter affected persons sometime during their practicing lifetimes. Whether these persons and their relatives are properly managed depends on a physician's familiarity with the manifestations of these disorders as well as with the genetic implications. Because several of these disorders predispose to carcinoma of the colon and rectum, the death of a patient or relative from cancer that might have been prevented at these sites represents a failure of medical care whether due to factors controllable by the patient, the physician or both.

Most of these disorders follow an autosomal dominant inheritance pattern so that they are not uniformly distributed in the population but are clustered in families. Recognition and proper diagnosis are hindered by poor history-taking, the preponderance of internal manifestations and the great variation of symptoms among affected persons, even among members of the same family.

Why genetic disorders involving autosomal dominant inheritance are so variable in their outward manifestations is by no means clear. This lack of understanding, however, is likely to persist because only about six disorders have been characterized at the molecular level. At present these clinical disorders are difficult to study quantitatively because of technical limitations on the nature, frequency and extent of methods of examining the largely internal structural changes.

Another factor contributing to the uncertainty and confusion among physicians in differentiating these disorders is the inclination of many investigators to "lump" them diagnostically despite possible distinguishing features that suggest genetic heterogeneity. A more appropriate approach is given in the article by Gardner and colleagues elsewhere in this issue. They discuss the most recent results of studies initiated by Dr. Gardner over 30 years ago.

Familial polyposis coli (FPC) has been known since the last century, but investigation of the Gardner syndrome (GS) as a separate entity began in 1947. Both segregate in an autosomal dominant pattern, vary substantially in the age of persons at onset, and are characterized by the presence of adenomatous polyps and a strong predisposition to adenocarcinoma of the colorectum. What, then, are the real differences between GS and FPC? Indeed, what is the evidence that they are really distinct and separate disorders? Some have proposed that FPC and GS represent points on a single spectrum, possibly at a single gene locus, and have even suggested logical but currently untestable genetic mechanisms to account for the observed variation. The evidence, however, still appears to weigh heavily in favor of their distinctiveness.

The distribution and numbers of adenomatous polyps are possible differentiating points. Although involvement in FPC had been thought to be limited to the colon and rectum, more recent evidence, especially from fiberoptic endoscopic studies, indicates that polyposis can occur in any portion of the gastrointestinal tract. Attention is focused justifiably on the colorectum because of the much greater tendency for adenocarcinoma to develop there.

McKusick[1] suggested that the colonic polyps in GS were fewer in number and more scattered than in familial polyposis coli. Bussey,[2] however, in describing the large number of patients in the St. Mark's Hospital Polyposis Register, found a wide range in number and distribution of polyps in colectomy specimens from FPC and GS patients, thus providing little support for the McKusick hypothesis. On the other hand, Gardner and colleagues conclude that their observations support the hypothesis.

Questions must be raised, however, about the roles of extracolonic manifestations of GS and of surgical intervention as possible confounding factors. It is clear from kindred 109 and other families that some GS patients have extragastrointestinal manifestations for years before colorectal polyps are detected. These largely external abnormalities could be signals leading to earlier diagnosis, especially in relatives of an affected patient. Hence, colectomy would be more likely to be carried out at an early stage when fewer, more scattered polyps are present. These possibilities are at least consistent with the observations. It is unfortunate that the observed difference is not the other way around, with FPC having fewer, more scattered polyps than GS, because then the tendency toward biased ascertainment would seem less likely to interfere.

Gardner and associates, as well as many other authors, feel that the extragastrointestinal lesions are the more distinctive features. Yet, as indicated by Bussey,[2] the harder that investigators look to find these characteristic GS lesions, the more likely they seem to be found in patients diagnosed as having FPC. This seems to be most true for osteomas, and least true of desmoid tumors as judged by the more recent literature. At the very least, these occurrences suggest that based on present diagnostic criteria, it may not be possible to distinguish between GS and FPC in some families, and that errors are made regularly. Regrettably, this situation is made worse by those authors who neither attempt to test possible distinctions nor clearly warn their readers that they are "lumpers" rather than "splitters."

One way out of this diagnostic quandary would be to identify in vitro one or more precisely measurable features that distinguish between the GS and FPC genes, assuming of course that they differ. Studies of growth characteristics of cultured skin fibroblasts, ploidy (multiples of the hormonal number of chromosomes) in cultured adenoma epithelial cells and cell kinetics in adenomas are so demanding technically that any putative distinctions identified would need confirmation in more than one laboratory.

A marker that is closer to the gene will be

necessary. The large and readily available kindreds as discussed by Gardner and colleagues could provide fertile ground for the application of recombinant DNA techniques in order to find, for example, a restriction enzyme cleavage site that is tightly linked to either the GS or FPC gene, but not to both. To date this has only been possible in the case of sickle cell anemia[3]; however, studies now in progress seem likely to yield other such instances. Or perhaps the critical distinctions are within the gene itself, with the recombinant DNA techniques yielding surprising insights into mutation in humans as has recently been found in one form of thalassemia.[4] If such an approach becomes feasible with the polyposis disorders, then diagnoses could be made at any age, using DNA from any nucleated cell—leukocytes and skin fibroblasts being convenient sources—and independent of the presence or absence of any manifestation of the genes. Until then we will need to be as careful as we can be in assessing and quantitating the differentiating features so nicely presented here in the article by Gardner and colleagues.

RICHARD W. ERBE, MD
Associate Professor of Pediatrics
Harvard Medical School
Chief, Genetics Unit
Children's Service
Massachusetts General Hospital
Boston

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